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Long Non-coding RNA Zinc Finger Antisense 1 (ZFAS1) Regulates Proliferation, Migration, Invasion, and Apoptosis by Targeting MiR-7-5p in Colorectal Cancer

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Colorectal cancer (CRC) is one of the most common tumors, the causes of which remain unclear. Recently, many kinds of long non-coding RNAs (lncRNAs) have been identified to have an important role in the biological function of CRC. However, the effect of lncRNA zinc finger antisense 1 (ZFAS1) on development of CRC is still incompletely clear.

Material/Methods: Firstly, the expression of ZFAS1 and microRNA (miR)-7-5p in 40 CRC tissues and adjacent tissues was measured by real-time polymerase chain reaction. Then, we detected the cell proliferation, migration, invasion, and apoptosis in CRC cell lines by using Cell Counting Kit-8 assay, colony formation assay, flow analysis, and Transwell assay, respectively. Then, the relationship between ZFAS1 and miR-7-5p was verified by luciferase reporter assay. Finally, rescue experiments were conducted to confirmed that interaction of ZFAS1 and miR-7-5p *in vitro*.

Results: Our results showed that ZFAS1 was upregulated in CRC tissues, correlated with overall survival rates, and negatively related to the expression of miR-7-5p. It was verified that miR-7-5p was a direct target of ZFAS1 by bioinformatics analysis and luciferase reporter assay. In addition, knockdown of miR-7-5p inhibited proliferation, migration, and invasion, and promoted apoptosis in CRC cell lines, which could be rescue by miR-7-5p inhibitor.

Conclusions: Our study indicated that ZFAS1 directly targeted miR-7-5p, and knockdown of it could inhibit tumor growth, migration, invasion, and induce apoptosis in CRC. These data might provide a potent treatment mechanism or promising biomarker for CRC.

MeSH Keywords: Cell Migration Assays • Cell Proliferation • MicroRNAs • RNA, Long Noncoding

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Background

Colorectal cancer (CRC) represents the one of the most common tumors, and is also the third highest morbidity and mortality rated cancer in the world, with about 1.3 million new cases each year [1,2]. The distribution of CRC burden varies extensively, where more than half of all cases and about 60% of all deaths are detected in developed countries; however, this tendency is changing due to improvements made in health systems and the implementation of screening program in developed countries in the last few years [3]. Although the cause of CRC remains unclear, it has been determined to be closely related to the following factors: dietary factors, genetic susceptibility, parasites, and precancerous conditions [2]. The development of CRC involves a series of transcriptional levels, post-transcriptional levels [4], and epigenetic changes [5], but the mechanism of the development of CRC has not yet been fully elucidated, and the treatment of CRC has not achieved the desired results [6]. Therefore, it is urgent to explore underlying mechanisms that participated in the pathogenesis of CRC, which might then provide new diagnostic and treatment methods for CRC.

Long non-coding RNA (lncRNA) is defined as an RNA molecule that might play a key role in transcription initiation or splicing transcription, which is distinguished based on its length of more than 200 nucleotides from the short traditional microRNAs (miRNAs) [1]. LncRNAs are also identified as being expressed at specific stages of biological growth and development, and being involved in a variety of life activities such as genome imprinting, X chromosome inactivation, chromosome modification, and telomere biology [7,8]. Recent studies have reported that lncRNAs can regulate gene expression at the transcriptional level and participate in the occurrence and development of various human diseases including tumors [9,10]. It has been determined that aberrant expression levels of lncRNAs play an extremely important role in the diversified malignant pathology of tumors, such as growth, invasion, and apoptosis [1,11]. In addition, lncRNAs usually act as a competing endogenous RNA (ceRNA), which can sponge relative miRNAs and regulate post-transcriptional expression of downstream targeting mRNAs. For instance, Dong et al. reported zinc finger antisense 1 (ZFAS1) could promote growth and invasion of renal cancer cells by targeting miR-10a/SKA1 pathway [12].

The lncRNA ZFAS1, which is at located at 20q13, has been found stably expressed in many kinds of tumors [13]. Increasing evidence has shown that ZFAS1 is upregulated and involved in occurrence and development of several tumors, such as bladder cancer [14], cervical cancer [15], prostate cancer [16], and breast cancer [17]. Many studies have also shown that ZFAS1 serves as an oncogene in cancers, which could promote cell proliferation and invasion and inhibit cell apoptosis via regulating downstream protein expression [18]. Nevertheless, the effect of ZFAS1 on clinical significances, biological functions, and related underlying mechanisms of CRC remains to be explored. In this study we firstly revealed that the pivotal functions of ZFAS1 in CRC progression by targeting miR-7-5p, which might provide a new target for the CRC treatment.

Material and Methods

Clinical specimens

There were 40 clinical CRC tissue specimens and corresponding cancers collected from the Affiliated Hospital of Chifeng University between December 2013 and July 2015. All specimens were frozen in liquid nitrogen and stored at –80°C. All cases were clearly diagnosed by histopathology and were excluded from the history of other malignant tumors. All patients with CRC received no chemotherapy or radiation before surgery. The present study was performed with the approve of the Research Ethics Committee of Affiliated Hospital of Chifeng University.

Cell culture and transfection

CRC cell lines (SW-620, HCT-116, DLD-1, SW480, and H29) and normal colonic cell line (NCM460) were purchased from the Institute of Biochemistry and Cell Biology of the Chinese Academy of Sciences (Shanghai, China). Cells were contained in Dulbecco's Modified Eagle Medium (DMEM, Invitrogen, USA) with 10% fetal bovine serum (FBS, Gibco, USA) at 37°C with 5% CO_2.

For transfection, siRNA of ZFAS1 (si- ZFAS1) and the negative control siRNA (si-NC) were synthesized by Genepharma (Shanghai, China). MiR-7-5p mimics, miR-7-5p inhibitor, and related negative controls were also purchased from GenePharma (Shanghai, China). Cells were first cultured in 24-well plates and then transfected by using Lipofectamine 2000 (Invitrogen, USA) according to the manufacturer's instruction. The cells were used for further experiments after 48 hours of transfection.

Quantitative real-time polymerase chain reaction (qRT-PCR)

Firstly, TRIzol reagent solution (Invitrogen, USA) was used to extract RNAs from CRC tissue and cells following the manufacturer's protocol. The cDNA was then synthesized using a reverse transcription kit (Thermofisher, USA) and PCR was performed on ABI7500 thermo-recycler (Applied Biosystems, USA). The relative expression level of the gene was calculated using the $2^{-\Delta\Delta}$Ct method. Each reaction was repeated 3 times. Primers for PCR amplification are shown in the Table 1.

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Table 1. List of primers used for real-time polymerase chain reaction.

Name of genes	Sequence (5'-3')
ZFAS1	Forward: AGCGGTTTGGTTAGAGCAGC
	Reverse: CACACTGGTACACGTGGCTC
miR-7-5p	Forward: TGTTGTTTTGTGAT
	Reverse: GTGCAGGGTCCGAGGT
U6	Forward: CACTG GGTGC GGCAG GT
	Reverse: TCATC ACCGA TCGA TACGA TGA
GAPDH	Forward: CACTCACGGCAAATTCAACGGCA
	Reverse: GACTCCACGACATACTCAGCAC

Cell growth assay

The cell growth was measured using Cell Counting Kit-8 (CCK-8) (Sigma, USA). The transfected cells (5×10^4 per well) were cultured in 96-well plates, following by the addition of CCK-8 solution, then cells were incubated at 37°C for 1 hour. We recorded the absorbance at 450 nm. The cell viability was tested by a Benchmark microplate spectrometer (Bio-Rad, USA) by using absorbance at 450 nm.

Colony formation assay

The transfected cells (5×10^2 per well) were seeded into 6-well plates. After 14 days of culture, the cells were fixed with 4% paraformaldehyde and then stained with 0.5% crystal violet and viewed using a light microscope (Nikon Corp. Japan). For the invasion assay, the membranes of each chamber were used to measure colonies formation.

Apoptosis analysis

The transfected cells (5×10^4 per well) were seeded into 6-well plates as described. The cells were stained by using an AnnexinV/propidium iodide kit (BD Biosciences, USA) according to the manufacturer's protocol. Next, the apoptosis rate of cells was detected by flow cytometry analysis and analyzed using a BD FACSCanto II system (BD Biosciences, USA).

Transwell assay

The cell invasion and migration assay was conducted by using 24-well insert Transwell chambers (Costar, USA). The transfected cells (1×10^4 per well) were firstly suspended in serum-free medium and then add to upper chamber or Matrigel-coated Transwell insert. The cultured medium in the bottom chamber contained 10% FBS. After 24 hours, the upper chamber was removed and cells on the filter membrane were wiped off with cotton swabs. After washing with phosphate-buffered saline (PBS), the chamber was fixed in 95% ethanol for 10 minutes, washed with PBS, and then stained with hematoxylin for 5 minutes. After washing with distilled water, the number of invaded and migrated cells were measured in 5 randomly fields.

Luciferase reporter assay

Bioinformatics analysis were firstly used to predict the potential miR binding sites of ZFAS1. Next, the wild-type or mutant ZFAS1 binding miR-7-5p was subcloned into a pGL3-basic vector (Promega, USA) to build the reporter vectors. Then, CRC cells (5×10^4 per well) were cultured in 24-well plate and co-transfected constructed luciferase plasmids. After 48 hours of transfection, cells were lysed and monitored the luciferase activity by a Dual-Luciferase Reporter Assay System (Promega, USA).

Statistical analysis

All data were represented as mean ± standard deviation (SD). The Statistical analysis was performed using SPSS 21.0 software (Chicago, IL, USA). The difference between groups were measured by Student's *t*-test and one-way ANOVA test. The correlation between the ZFAS1 and miR-155-5p expression was explored by Pearson's correlation analysis. The association between ZFAS1 and overall survival was analysis by Kaplan-Meier and log rank test. $P<0.05$ was considered to be statistically significant.

Results

The highly expression of ZFAS1 in CRC

Firstly, we analyzed ZFAS1 expression in 40 CRC tissues and adjacent tissues by RT-PCR. Our results found that the expression of ZFAS1 in CRC tissues was dramatically upregulated compared to adjacent tissues, and reached levels of more than 4 times that of the corresponding tissues (Figure 1A, 1B). In order to further evaluated the correlation between overall survival and ZFAS1 expression, we then divided the patients into 2 groups based on the expression of ZFAS1. Our results showed that a poor overall survival appeared in the higher ZFAS1 expression group compared with the lower ZFAS1 expression group by 36 months follow-up (Figure 1C). In addition, we discovered that ZFAS1 was also upregulated in CRC cell lines (SW-620, HCT-116,DLD-1, SW480, and H29) compared with normal colonic cell line (NCM460) (Figure 1D). Our results suggested that ZFAS1 might be involved in CRC occurrence and development.

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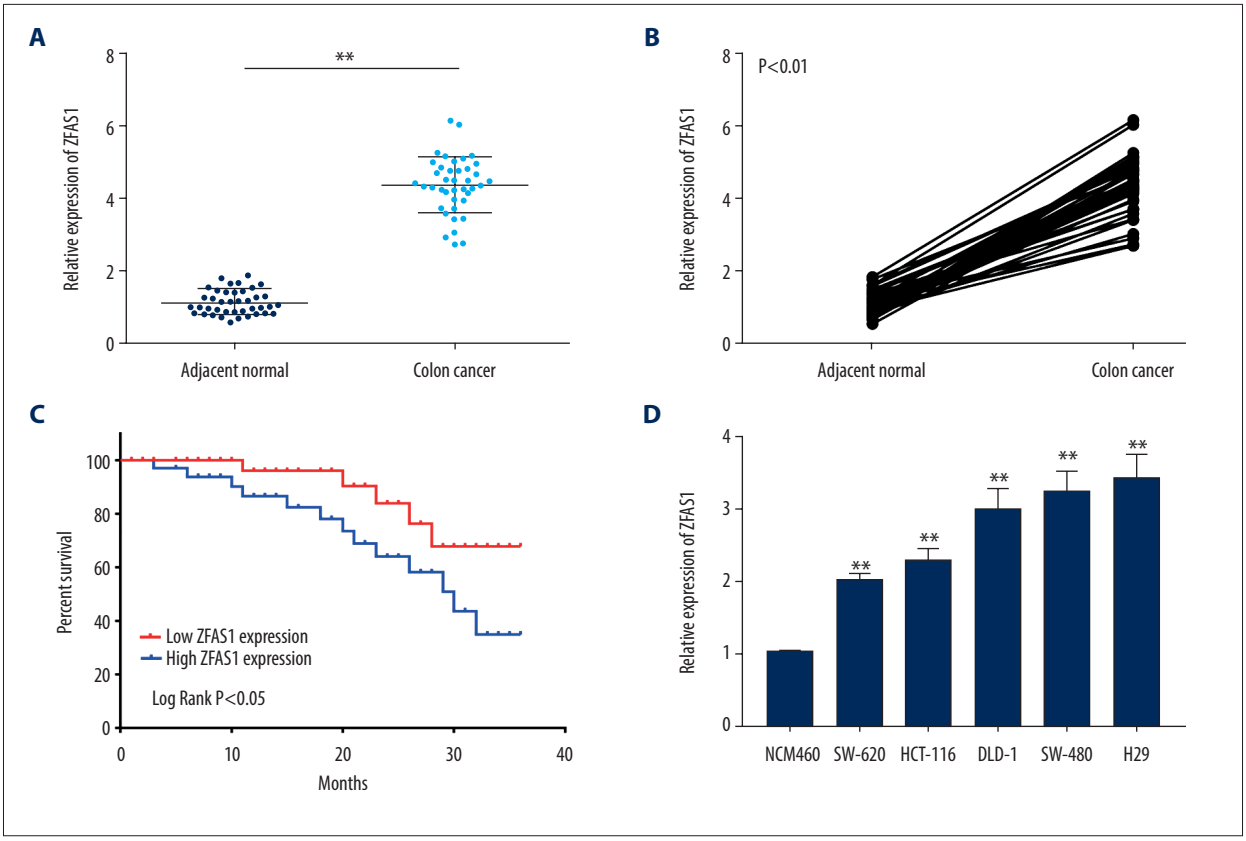

Figure 1. The high expression of ZFAS1 in colorectal cancer (CRC). (**A, B**) Relative expression of ZFAS1 in CRC tissues and para-cancer tissues. (**C**) The correlation between ZFAS1 expression and overall survival in CRC patients (**D**) Relative expression of ZFAS1 in CRC cell lines. * *P*<0.05, ** *P*<0.01 versus control. ZFAS1, zinc finger antisense 1.

Inhibition of ZFAS1 suppressed proliferation, invasion, and migration, and promoted apoptosis of CRC *in vitro*

To detect the biological mechanism of ZFAS1 in CRC, we silenced the ZFAS1 in SW480 and H29 cell lines by using si-ZFAS1, and the efficacy of ZFAS1 knockdown was detected by qRT-PCR (Figure 2A). As shown in Figure 2B, the cell proliferation was inhibited in CRC cell lines when transfected with si-ZFAS1. We then performed colony formation assay to survey the inhibitory effect of ZFAS1 on clone formation ability. Our results showed that knockdown of ZFAS1 effectively inhibited the clone formation ability *in vitro* (Figure 2C). At the same time, we also found that the apoptosis rate in CRC cells were significantly increased after silencing expression of ZFAS1 when compared to control cells (Figure 2D). In addition, transfection of si-ZFAS1 into CRC cells could suppress invasion and migration ability when compared with the control group (Figure 2E). Therefore, ZFAS1 knockdown significantly inhibited the proliferation, invasion and migration, and promoted apoptosis in SW480 and H29 cell lines.

ZFAS1 was a direct target of miR-7-5p.

Accumulating evidence has suggested that lncRNAs can act as a ceRNA by binding to specific miRNAs. Thus, we conducted bioinformatics analysis to predict whether ZFAS1 plays a role in such a way. As displayed in Figure 3A, we found miR-7-5p possessed complementary binding sites with ZFAS1. Before the verification test, we detected efficacy of miR-7-5p over-expression or down-expression by qRT-PCR (Figure 3B). The relationship between miR-7-5p and ZFAS1 was subsequently confirmed by the dual-luciferase reporter assay, and it was illustrated that miR-7-5p over-expression evidently reduced the luciferase activity, and miR-7-5p knockdown promoted that of the ZFAS1-wt luciferase reporter vector. However, both of miR-7-5p mimics and inhibitor group could not affect the luciferase activity of ZFAS1-mut (Figure 3C). Further, we revealed that downregulation of ZFAS1 strictly promoted expression of miR-7-5p in CRC cell lines (Figure 3D). To more precisely detect the relationship between miR-7-5p and ZFAS1, we detected the expression of miR-7-5p in CRC tissues by RT-PCR. Our findings indicated that expression of miR-7-5p was decreased in CRC tissues in comparison with adjacent tissues (Figure 3E). Additionally, expression of ZFAS1 and miR-7-5p

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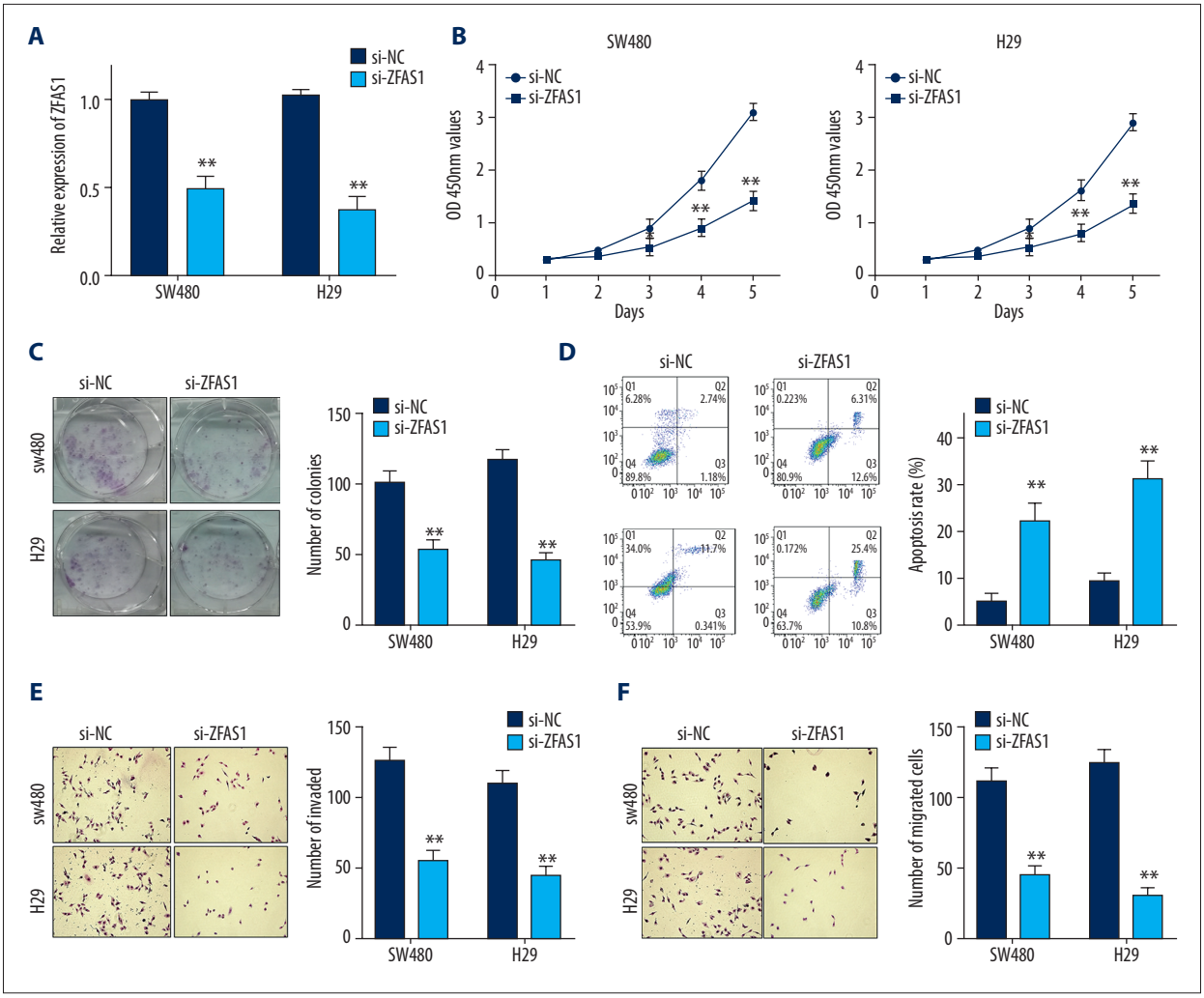

Figure 2. Inhibition of ZFAS1 suppressed proliferation, invasion, and migration, and promoted apoptosis of colorectal cancer (CRC) *in vitro*. (**A**) qRT-PCR was performed to validate the efficiency of si-ZFAS1. (**B**) The proliferation rate of knockdown ZFAS1 SW480, and H29 cells measured by CCK-8 assay. (**C**) The clone formation of knockdown ZFAS1 SW480 and H29 cells were detected by colony formation assay. (**D**) Flow cytometry was performed to detect the apoptosis of knockdown ZFAS1 SW480 and H29 cells. (**E, F**) Transwell assay accessed invasion and migration in knockdown ZFAS1 SW480 and H29 cells. * $P<0.05$, ** $P<0.01$ versus control. NC – negative control; ZFAS1 – zinc finger antisense 1; qRT-PCR – quantitative real-time polymerase chain reaction; CCK-8 – Cell Counting Kit-8.

in CRC tissues had a negatively correlation (Figure 3F). These results suggested that ZFAS1 was a direct target of miR-7-5p.

MiR-7-5p reversed the effect of ZFAS1 on CRC tumorigenicity

To better understand the relationship between miR-7-5p and ZFAS1 in biological functions of CRC, we conducted rescue experiments by downregulation of miR-7-5p expression in ZFAS1 knockdown CRC cells lines. Our results found that the miR-7-5p inhibitor could partly relieve growth inhibitory effect of ZFAS1 knockdown in CRC cells, which was examined by CCK-8 assay and colony formation assay (Figure 4A, 4B). In addition, we found that miR-7-5p inhibitor could rescue the facilitated effect on apoptosis in ZFAS1 knock downed CRC cells (Figure 4C). In addition, Transwell assay indicated that miR-7-5p inhibitor could elevated invasion and migration ability in SW480 cell, which were suppressed by the down-expression of ZFAS1 (Figure 4D, 4E). Together, these results suggested that down-expression of ZFAS1 might regulate biologic functions of CRC by targeting miR-7-5p.

Discussion

CRC is recognized as having one of the highest mortality rates of human tumors, causing great harm to human health [19].

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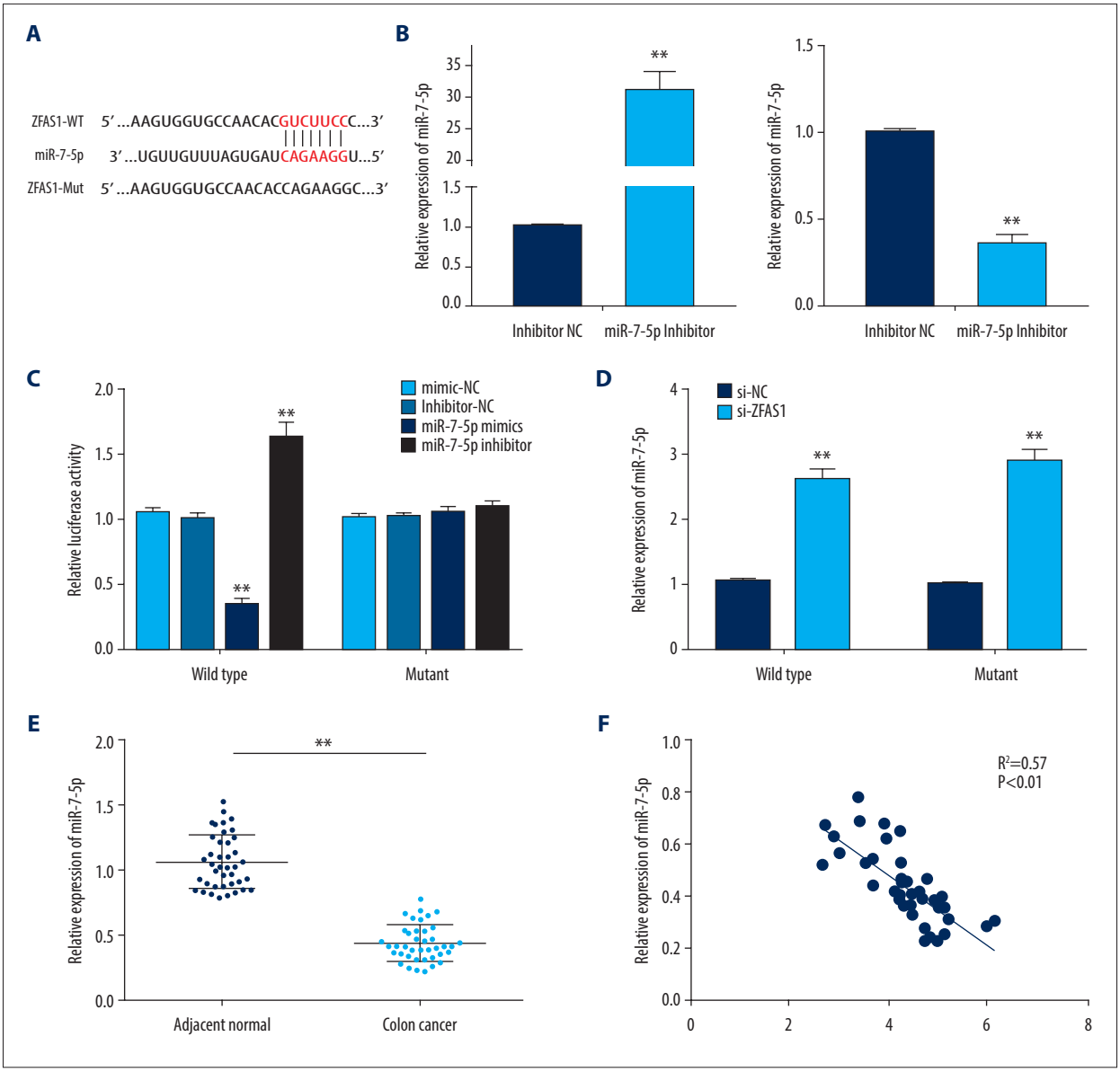

Figure 3. ZFAS1 was a direct target of miR-7-5p. (**A**) Putative binding sites of miR-7-5p within the ZFAS1 predicted by bioinformatics analysis. (**B**) The upregulated and downregulated efficiency of miR-7-5p was validated by qRT-PCR. (**C**) The correlation between ZFAS1 and miR-7-5p was detected by luciferase reporter assay. (**D**) The miR-7-5p expression in SW480 and H29 cells transfected with si-ZFAS1. (**E**) Relative expression of miR-7-5p in colorectal cancer (CRC) tissues and para-cancer tissues. (**F**) Pearson's correlation analysis was performed to evaluate miR-7-5p and ZFAS1 expression in CRC tissues. * $P<0.05$, ** $P<0.01$ versus control. NC – negative control; ZFAS1 – zinc finger antisense 1; qRT-PCR – quantitative real-time polymerase chain reaction; CCK-8 – Cell Counting Kit-8.

In China, with the increase in people's material living standards, pollution of land and water resources, and aging of the population, the incidence and mortality of CRC have shown an upward trend in recent years [20]. Although a large amount of work has been done on the pathogenesis of CRC, the etiology may well be highly related to the following factors: dietary factors, generally considered to be high-fat, high animal protein and low-fiber diet; and genetic susceptibility [21]. Due to the limitations of effective diagnostic and treatment techniques, patients with CRC usually have poor prognosis [19,22]. Therefore, relying on basic research to explore new reliable noninvasive early diagnosis and treatment methods is an important direction for current research [23].

LncRNAs, usually refers to a class of RNA with a molecular weight of more than 200 nucleotides [24]. Recent studies have

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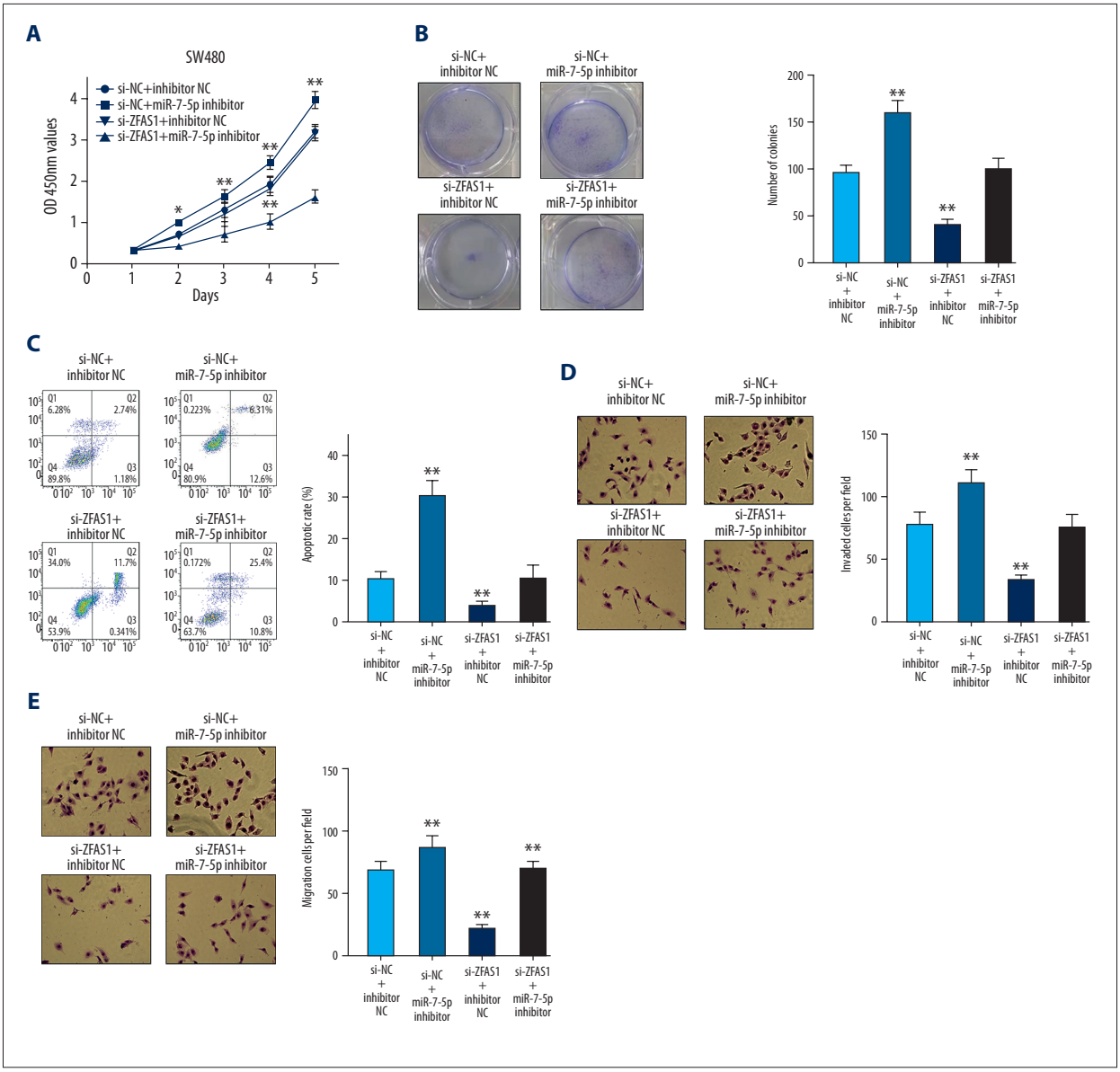

Figure 4. MiR-7-5p reversed the effect of ZFAS1 on colorectal cancer (CRC) tumorigenicity. (**A**) The proliferation of knockdown ZFAS1 SW480 and H29 cells transfected with inhibitor-NC and miR-7-5p inhibitor were measured by CCK-8 assay. (**B**) The colony formation assay was performed to accessed clone formation of knockdown ZFAS1 SW480 and H29 cells transfected inhibitor-NC and miR-7-5p inhibitor. (**C**) The effect of knockdown ZFAS1 SW480 and H29 transfected with inhibitor-NC and miR-7-5p inhibitor on apoptosis. (**D, E**) Transwell assay detected invasion and migration of knockdown ZFAS1 SW480 and H29 cells inhibitor-NC and miR-7-5p inhibitor. * $P<0.05$, ** $P<0.01$ versus control. NC – negative control; ZFAS1 – zinc finger antisense 1; CCK-8 – Cell Counting Kit-8.

indicated that lncRNAs participate in a variety of biofunction activities such as genome imprinting, X chromosome inactivation, chromosome modification, and telomere biology [25]. LncRNAs can also modified targeting gene expression at the transcription level or post-transcriptional level, and the epigenetic level which is involved in the occurrence and development of various human diseases such as malignant tumors, coronary heart disease, Alzheimer's disease, and diabetes [26].

Emerging studies have found multiple regulatory relationships between lncRNAs and tumors, indicating that lncRNAs play an important part in biological function of tumors such as proliferation, invasion, migration, and apoptosis [27–29].

ZFAS1 is a newly discovered lncRNA firstly described by Askarian-Amiri et al., and it is highly expressed in mammary gland tissue and has low expression in breast cancer tissue,

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thus it is inferred that ZFAS1 might be a suppressor gene in breast cancer [30]. However, other studies have shown that the expression of ZFAS1 was distinctly upregulated in ovarian cancer and related to survival, and could abolish its target gene *SP1* by binding to miR-150 [27]. Current evident has indicated that ZFAS1 might act as a novel target and prognostic factor for the treatment of CRC [31], for instance, Ansari et al. revealed that ZFAS1 allocated maximum alteration among the CRC samples and correlated with overall survival in patients [32]; Yan et al. showed that ZFAS1 might serve as an oncogene by regulating its downstream target ZEB1 to promote epithelial-to-mesenchymal transition in CRC [33]. In our present study, we revealed that ZFAS1 was increased in CRC tissues compared with adjacent tissues, and had a close correlation with overall survival in CRC patients. Our data also indicated that ZFAS1 knockdown could significantly inhibit proliferation, invasion, and migration, and induce apoptosis in SW480 and H29 cell lines. That means that ZFAS1 might function as an oncogene to promote tumorigenesis of CRC, which is a similar finding with previous research.

A number of studies have elucidated that lncRNAs can completely bind with target miRNAs, which can affect the expression of downstream genes [25]. Several studies have revealed that ZFAS1 functions as a migration and invasion activator in tumorigenesis through suppression of miRs, which provides evidence that ZFAS1 might be a potential effective molecular target for cancer therapy; Wang et al. revealed that ZFAS1 contributed to tumorigenesis of bladder cancer via a functional regulatory network of ZFAS1 sponging miR-329 [34]. Li et al. demonstrated that ZFAS1 acted as an oncogene and ceRNA for miR-486 in osteosarcoma tumorigenesis [35]. Dong et al. found that ZFAS1 served as a promoter for renal cell carcinoma growth and metastasis by targeting the miR-10a/SKA1 pathway [12]; Chen et al. also reported that SP1-induced ZFAS1 took part in CRC progression by modulating miR-150-5p and VEGFA expression [36]. In our research, we firstly validated miR-7-5p was a potential target for ZFAS1 in CRC tissues and cell lines. Our data also identified that the expression of ZFAS1 and miR-7-5p had a negative correlation in CRC tissues. Further, ZFAS1 silence could evidently promote miR-7-5p expression *in vitro*. Therefore, we speculated that miR-7-5p was a direct target of ZFAS1, and might have an interaction effect on biological functions in CRC.

Previous studies have shown that miR-7-5p usually acts as a tumor suppresser in bladder cancer, breast cancer, CRC, and glioblastoma. In colon cancer research, Dong et al. reported that miR-7-5p could inhibit the proliferation and migration of CRC cells by negatively regulating KLF [37]; Yu et al. indicated that miR-7-5p and TINCR might work as a ceRNA mechanism, modulating CRC progression via the PI3K/Akt/mTOR signaling pathway [13]. Liu et al. also showed that lncRNA RP4 also functioned as a ceRNA for miR-7-5p in the pathogenesis of CRC which could be a potential therapeutic target for CRC treatment [38]. However, the related roles between miR-7-5p and ZFAS1 in CRC have not been reported until now. We firstly found that the detected miR-7-5p expression was downregulated in CRC tissues and negatively correlated with ZFAS1. In addition, our results showed that silenced miR-7-5p could reverse the biological progression induced by knockdown ZFAS1 in CRC cells. Therefore, our findings suggested knockdown ZFAS1 could suppress CRC progression by completely binding to miR-7-5p.

Conclusions

Our study found that ZFAS1 was upregulated in CRC tissues and cells lines, which related with overall survive in CRC patients. We also indicated that ZFAS1, served as a miR-7-5p sponge, and knockdown of it could inhibit tumor growth, migration, and invasion, and induce apoptosis in CRC. Therefore, the results from our study might provide a potent treatment mechanism or promising biomarker for CRC.

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